REMARKS

Claim 53 has been amended to delete the phrase "an organic molecule less than 2000 daltons and comprises a homocyclic aromatic radical, a heterocyclic aromatic radical or a heterocyclic radical," which was the basis of the new matter rejection. Instead claim 53 now recites the term "small organic molecule" which has been examined in previous claim amendments, without being rejected. Claim 53 also recites that "the CTBFs are sufficiently soluble in aqueous solutions to be tested for their ability to bind to a target biological molecule." This is based on the last sentence of paragraph [0072] of the published application, which states that "virtually any small organic molecule that is capable of being chemically coupled to another small organic molecule may find use in the present invention with the proviso that it is sufficiently soluble in aqueous solutions to be tested for its ability to bind to a target biological molecule."

New claims 67 and 79 are supported by the second sentence of paragraph [0073] of the published application, which states that "Candidate target binding fragments that find use herein will generally be less than about 2000 daltons in size, usually less than about 1500 daltons in size, more usually less than about 750 daltons in size . . ."

New claims 68-69 and 73-74 are supported by the second sentence of paragraph [0072] of the published application.

New claims 70 and 75 are supported by Figure 2 of the present application.

New claims 71-72 and 76-77 are supported by the first sentence of paragraph [0074] of the present application.

New claims 78-89 recite "fragment" instead of "candidate target binding fragment." The word "fragment" finds support from the phrase "candidate target binding fragment."

Statement of the Substance of the Interview

Applicants wish to thank the examiner for the telephonic interview on October 12, 2005 in which all of the claims were discussed, in particular independent claim 53 in relation to the outstanding rejections for lack of written description and obviousness over Kirkpatrick in light of Silverman. An agreement was not reached during this interview and applicants' main positions discussed during the interview are reflected in the remarks of this response.

Priority

The examiner stated that "the filing date of the present application is deemed to be the filing date of 60/253,629, which is December 28, 2001." Applicants note that the present application never claimed prority to 60/253,629. Moreover, applicants have overcome the new matter rejection. Therefore, applicants are entitled to a priority date of March 26, 1999, which is the filing date of the parent CIP application. Accordingly, the rejections of the outstanding office action at page 21 for new matter and page 22 for anticipation/obviousness are rendered moot.

Rejection for Lack of Written Description

According to MPEP § 2163.02, "[a]n objective standard for determining compliance with the written description requirement is, "does the description clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed." *In re Gosteli*, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989). Applicants contend that anyone of skill in the art would be able to recognize that applicants did invent what is claimed. All of the library members of claim 53 have the distinguishing chemical structure CTBF-S-S-R^8, which is describe in the specification. All of the library members have the -S-S-R^8 moiety, which is a chemical formula.

A. Applicants have Evidenced that the Skilled Artisan Clearly Recognizes their Invention

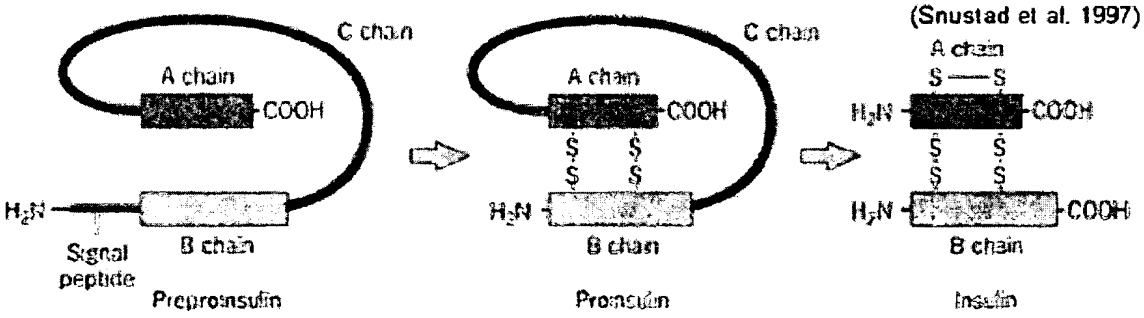
The attached 132 Declaration by Dr. Clinton Kruger (Exhibit 1) provides direct evidence, that a person of skill in the art does indeed recognize that the applicants invented what is claimed. In this Declaration, Dr. Kruger states that he "find[s] the claimed library sufficiently described in paragraphs 148 (general description of R^8) and 221 (general description of the disulfide containing library) of US 2002/0115107." See Item 4.

Dr. Kruger also states that he can distinguish the present invention from other libraries. "Because of the presence of a common feature, -S-S-R^8, this library is distinguishable from others such as those described by Roland E. Dolle, Comprehensive

Survey of Combinatorial Library Synthesis: 1999, *Journal of Combinatorial Chemistry* **2**: 383-433 (2000)." (Exhibit 2).

B. The Lilly facts are not Analogous to the Present Application

In *Lilly*, a rat cDNA sequence was found not to provide written description support for an entire class of vertebrate insulin. The way insulin is produced in the body makes it impossible to know the structure of insulin based on the amino acid sequence. This is because the protein encoded by the cDNA is actually preproinsulin (110 amino acids), which is enzymatically cleavage to produce proinsulin (86 amino acids), which is again cleaved to produce insulin (51 amino acids). See *Lilly* at p. 1564 and the below illustration, as illustrated on Dr. Steven Carr's website, (Exhibit 3), Department of Biology, Memorial University of Newfoundland.



preproinsulin → proinsulin → insulin
(110 aa's) (86 aa's) (51 aa's)

Two entire peptide sequences are excised from the peptide sequence encoded by the coding polynucleotide. Due to enzymatic cleavage, it is impossible to know or recognize the length or coding sequence of insulin cDNA or its corresponding mRNA. Therefore, the single rat cDNA, which actually codes for preproinsulin, could not provide any distinguishing characteristics for a genus of polynucleotides of unknown length and unknown sequence. Without more than a single species described, one of skill in the art would not have recognized any of the features of a genus of vertebrate cDNA. Would human cDNA encode for 100, 110 or 140 amino acids? What would be the sequence of the cleaved amino acids? How would the human insulin cDNA sequence differ from pig insulin cDNA, insulin frog

cDNA or insulin trout cDNA or any other vertebrate insulin cDNA? With only one species described, one of skill in the art could not answer these questions and thus envision the claimed genus.

Applicants also note that the claims of *Lilly* were directed to coding sequences. Even a single nucleotide that is miscoded, added or omitted can alter the encoded end protein, rendering the encoded protein nonfunctional. See Stryer (Exhibit 4). (A single altered amino acid in the beta chain of hemoglobin causes sickle cell anemia.) Also see Lazar (Exhibit 5). (Replacement of aspartic acid at position 47 with serine or glutamic acid sharply reduced biological activity of transforming growth factor-α.) In contrast, the present invention relates to a combinatorial library, which is used to assay large numbers of compound to determine their binding to a particular target. Whether or not a CTBF-S-S-R^8 compound binds to a target, it has provided useful information. Either a negative result or a positive results provides useful information for scientific research related to the CTBF-S-S-R^8 and its target. This contrasts sharply to precision required for a nucleotide sequence to be translated into a biologically functional coding sequence.

C. The Present Claims do Recite Identifying Chemical Structures and Physical Properties

In contrast, the present claims do have a distinguishing identifying chemical formula, which is CTBF-S-S-R^8. Also, the CTBFs are defined by physical characteristics (small, organic and water soluble). This distinguishes the present invention from CTBFs without a -S-S-R^8 moiety and that are not small, organic or water soluble. Any library whose members have this structure would be recognizable to one of skill in the art as being the invention of the applicants. The court in *Lilly* opined that "the name cDNA . . . conveys no distinguishing information" and "there is no further information in the patent pertaining to that cDNA's relevant structural or physical characteristics." The facts of *Lilly* do not square with the present claims, which do have distinguishing information, and the specification, which does disclose relevant structural and physical characteristics. In Figure 2, applicants have provided examples of 29 species possible CTBFs.

D. Combinatorial Chemical Libraries were Known in the Art as of the Filing Date

Moreover, at the time of filing of the present application, there were already known combinatorial libraries to be in existence, which contrasts with the facts of Lilly where there were no known insulin cDNA sequences in the prior art. For instance, as indicated in the

specification, applicants have indicated in the specification that commercial catalogs are handy sources of CTBFs. As noted in the attached pages from Delvin 1997, (Exhibit 6) the Aldrich chemical company (mentioned at pagraph [0073] of the present application) "drew upon 30,000+ compounds" available as test compounds for combinatorial libraries. Eleven other commercial suppliers of compound libraries are mentioned, with tens of thousand, even 400,000 structures available for libraries.

Moreover, according to Dolle, Journal of Combinatorial Chemistry, by the year 1998, 683 combinatorial libraries were publicly "abstracted along with their generic structures" in the review series published by this journal. Examples of the libraries are detailed in the Dolle article. Moreover, Terret 1998 (Exhibit 7) states that "[t]he average pharmaceutical company archive contains in the region of 200,000 compounds."

E. Binding Properties Would not Have Had to be Known *A Priori* in order for the Skilled Artsian to Recognize the Claimed Library

The real issue is not whether one of the skill in art would know binding properties *a priori* but whether one of skill in the art would be able to recognize a library of small organic molecules, all with the S-S-R^8 moiety. A "candidate" target binding fragment is only a fragment that might potentially bind to a target. Candidates are selected for assaying against biological molecules in accordance with what the target biological molecule is and the strategy behind the assay. If those of skill in the art knew in advance what binding fragment would bind to a biological molecule, there would be no need for libraries of compounds to assay against target molecules. In other words, it is the very nature of combinatorial libraries that the binding properties will not be known with certainty in advance. Hence, the use of the term "candidate" to modify target binding fragment.

Applicants also offer new claims 78-89 for the examiner's consideration, wherein the term "fragments" has been recited instead of the term "candidate target binding fragments." Claims 78-89 thus present a claim set that is devoid of an alleged functional terminology. The term fragment is present in the original specification and does not constitute new matter. Whether or not the moiety bonded to -S-S-R^8 is termed a candidate target binding fragment or simply a fragment is a (1) small, (2) organic molecule, (3) water soluble, and (4) bound to -S-S-R^8. Properties (1)-(4) are all structural, physical properties (not functional) that distinguish the claimed library from other materials, other molecules other libraries.

In conclusion, applicants contend that they have conveyed with reasonable clarity that they were in possession of a library of small organic molecules bound to -S-S-R^8.

Rejections for Obviousness

The examiner has argued that applicants' arguments with respect to the obviousness rejection are not commensurate with the scope of the claims. Applicants have addressed this point by amending the claims to recite that the members of the library are sufficiently soluble in aqueous solutions to be tested for their ability to bind to a target biological molecule. Therefore, the members of the library are limited to compounds that are soluble in aqueous solutions. Also for the following reasons, applicants urge that the combination of Kirkpatrick and Silverman does not render the present invention obvious.

A. Kirkpatrick did not Combine Compounds

No where in the Kirkpatrick reference is there a suggestion of combining members of the library. As Dr. Kruger states, the compounds of Kirkpatrick were "made using parallel combinatorial chemistry (col. 22, lines 49-53). This kind of synthesis makes each compound in its own reaction vessel and thus relies on automation to achieve increased synthetic productivity."

B. Applicants have Provide Direct Evidence Against Motivation

The 132 Declaration by Dr. Kruger evidences that one of skill in the art would not have been motivated to arrive at the present invention. Dr. Kruger states "[h]aving invested the time and effort to make the asymmetric disulfide compounds using parallel synthesis, it is unlikely that a person skilled in the art would take these individual compounds and combine them given that testing pure compounds is the most quantitative and robust method of screening that was then known." Therefore, applicants have provided evidence that one of ordinary skill in the art would not have been motivated to combine library members.

C. Bioisoteric Properties Cannot be Predicated *A Priori*

Applicants have attached a 132 Declaration by Dr. Clinton Kruger addressing the examiner's use of the Silverman reference. As supported by the attached Declaration, and the Patani, Chem. Rev. 1996 (Exhibit 8) "there is no consensus that an amino is an isostere for chloro or hydroxy."

Dr. Kruger concludes "even if one were to accept the proposition that an amine is isosteric or even bioisosteric with hydroxy or chlorine, based on the nature of the functional groups alone, a person of skill in the art would not have any expectation that an amine counterpart of a chloro or hydroxy-containing compound would have similar overall properties." Moreover, this conclusion of Dr. Kruger "does not contradict with the English translation of Buchi J." The last portion of the Kruger Declaration discusses the unpredictability of the biological properties of amino, methyl and chloro analogs, depending on whether the compounds are being used *in vivo* or *in vitro*.

As noted by the Silverman reference and Dr. Kruger, making an bioisosteric replacement will change the properties of a molecule. What the resulting effect will be, however, depends on the molecule changed and the context in which the change occurred. The results of such change cannot be reasonably predicted *a pirori* but can only be know by empirical data. Therefore, contrary to the examiner's assertions, there is no teaching that one of ordinary skill in the art would be able to reasonably expect the results of substituting chloro with amino in the context of the Kirkpartrick reference. The examiner's position seems to amount to a confusion between obvious to try (an improper standard) and obvious to do.

Finally, the attached Freidman 1951, (Exhibit 9), reference provides a comprehensive view of the effects of isosteric replacement on biological activity. Friedman classifies Cl, OH and NH_2 as "Class 1" isosteres. See Chart 5, page 302. With respect to "General Conclusions to Class 1," Friedman states "it is not possible to predict when members of this class will be bio-isosteric; in most instances they will not be." Paragraph 3, page 303. Thus even though Cl, OH and NH_2 might be classified in some schemes as isosteres "it is not possible to predict" whether these compounds will be bio-isosteres.

In light of the above evidence, i.e. the 132 Declaration and the teachings of Friedman, applicants submit they have rebutted the examiner's argument that Silverman stands for the proposition that "'classical' substitutions are routinely made by chemists of [ordinary] skill in the art" at a level that one can "reasonably expect to be successful." As evidenced by Freidman and Dr. Kruger, it is not possible to predict *a prior* what biological effect substituting chloro with amino will have.

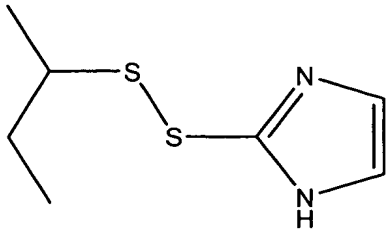
D. The Teachings of the Kirkpatrick References are not Being Viewed as a Whole

It is unclear as to how upon reading Kirkpatrick, one of ordinary skill in the art, without the hindsight benefit of the present specification would arrive at the present invention. Kirkpatrick disclosed and claimed compounds that were disulfide inhibitors of the cellular the thioredoxin redox couple (TR/Trx), which Kirpatrick was interested in because the "TR/Trx system appears to play an important role in human cancer." (Col. 9, lines 59-60.) Kirkpatrick was interested in finding compounds to treat cancer, not in general to improvement in combinatorial libraries.

When Kirkpatrick ran the tests of Tables 4, 5, and 6, he combined 24 R compounds of Figure 9 with the 17 R' compounds of Figure 10 or combine the 11 compound of Figure 11 with the 24 R compounds of Figure 9. Thus, rather than suggesting creating a library wherein one portion of the disulfide molecule is a fixed defined moiety (as in R^8 of the present claims), Kirkpatrick taught that the R and R' groups should be varied.

Figure 10 discloses 17 compounds, only which is a linear alkyl substituted with a chloro, i.e. "H moiety," which is the basis for the examiner's rejection. Kirkpatrick made both disulfides and bisdisulfides. Thus, without any hindsight from the present specification, one of ordinary skill in the art would upon reading Kirkpatrick, first either choose to make a library of disulfides or bis disulfides. On a statistically basis, the chance of choosing disulfides is (0.5). Then the artisan of ordinary skill, if looking at Figure 10, would choose one compound out of 17 total compounds. This is 1/17 or (0.0588). Therefore, the chances of choosing to make a disulfide with moiety H is: (0.5)*(0.0588)= (0.029). Stated another way, without hindsight from the present specification, on a mechanical basis (i.e. a basis devoid of inventive reasoning), one of skill in the art would be 97% likely not to choose to make a disulfide with the "H moiety" of Figure 10. And if one were to select the "H moiety" of Figure 10, it seems 100% certain, based on the teaching of Kirkpatrick, that one would not synthesize an entire library based only on the "H moiety," but rather test different moieties from Figure 10.

Kirkpatrick presents data to only four compounds tested in vivo, which were III-2, IV-2, VI-2 and DLK-36 and expressly refers to IV-2 as "the lead compound," which means that compound IV-2 was the most promising compound. See column 17, line 10. The lead compound IV-2 of Kirkpatrick has the following structure:



(III)

It is noteworthy that none of the compounds tested in vivo, that is compounds III-2, IV-2, VI-2 and DLK-36, where alkyl substituted compounds. See Table 1. Based on the results of Kirkpatrick, if one of ordinary skill in the art were somehow to have been motivated to test more compounds, the teachings of Kirkpatrick would have directed one of ordinary skill to assay unsubstituted alkyls rather than substituted alkyls.

Therefore in conclusion, applicants urge that the Kirkpatrick disclosure, when viewed as a whole, would not have motivated one of skill in the art to arrive at the present invention, alone or when combine with Silverman, which gives a brief introduction to the unpredictable field of isosteres and bioisosteres.

Conclusion

Accordingly, applicants urge that the present claims to be in condition for allowance. The Examiner is invited to contact the undersigned by telephone to advance prosecution of this application.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by a check being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741.

Respectfully submitted,

April 20, 2006
Date

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